WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101 • (610) 902-3710 • FAX: (610) 964-5973 Division of American Home Products Corporation

VERN G. DEVRIES, Ph.D.
ASSISTANT VICE PRESIDENT
U.S. REGULATORY AFFAIRS

September 9, 1999

Dockets Management Branch
Food and Drug Administration
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: {Docket No. 99N-0193}
Proposed Rule: Supplements and Other Changes to an Approved Application

Dear Sir or Madam:

On behalf of American Home Products, a diversified manufacturer of pharmaceutical, over-the-counter and biological drug products, we welcome the opportunity to comment on the Proposed Rule: Supplements and Other Changes to an Approved Application. This letter represents the combined comments of Wyeth-Ayerst Laboratories, Wyeth-Ayerst Research, Whitehall-Robins Health Care, ESI-Lederle, Wyeth-Lederle Vaccines and Pediatrics, and Genetics Institute.

The Food and Drug Administration's (FDA) proposed language from the Federal Register notice is italicized in this letter and identified by section. Our suggestions for revised language appear in standard type.

General Comments:

The Agency's proposed rule imposes additional regulatory burdens on applicants in reporting changes to an approved application. Examples of these increased reporting requirements are given herein. It is our opinion that these new regulatory requirements are beyond the intent of Congress, when it drafted and approved the "Food and Drug Administration Modernization Act of 1997" (FDAMA). We ask the Agency to revise the proposed rule to remove the additional regulatory burdens and issue a rule in keeping with Congress' intent.

§314.3(b)
* * * * *

Validate the effects of the change means to assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug.

We recommend that the word "assess" replace the word "validate" and "determine" replace "assess" in this section to read: **Assess** the effects of the change means to **determine** the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug.

99N-0193

C 14

Rationale: Although FDAMA, Section 116, uses the words "validates the effects of the change" we believe the word "validate" should be reserved for its usage within the context of the Good Manufacturing Practices usage, *i.e.*, the validation of products and equipment. The words "validate" and "validation" should be avoided throughout the entire proposed rule and in its place, assess or assessment, respectively, should be used. This would help clarify the meaning of the term and avoid confusion, especially where documentation for validating the effects of the change is required for submission to an application. FDA should clarify that "validation reports" of GMP product validation required prior to distribution of the product to the marketplace are not the kind of documents FDA expects to see submitted in a supplement or an annual report for a change being reported to an approved application.

***§ 314.70 (a)(6)**: A supplement or annual report shall include in the cover letter a list of all changes contained in the supplement or annual report.*

We recommend that the words "or annual report" be deleted to read: A supplement shall include in the cover letter a list of all changes contained in the supplement.

The requirement to include a cover letter describing all the changes made in an annual report represents an additional regulatory burden. Currently, annual reports only require submission of form FDA2252 with the annual report. We recommend that the FDA revise form FDA2252 to include a box along each section of the form, which can be checked off by the applicant, if changes are being reported for that section. This would be in keeping with the policy on paperwork reduction and meet FDA's need for determining that changes are being reported in the annual report. FDA already requires that a SUPAC change be so noted on form FDA2252 for annually reportable changes (Refer to Roger L. Williams' letter to Industry of April 11, 1996, attached).

***§ 314.70(b)(2)(iii)**: Changes that may affect product sterility assurance, such as changes in product or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation*

Insert the word "adversely" before "affect" to read: Changes that may **adversely** affect product sterility assurance, such as changes in product or components sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation;

Rationale: The only criterion for a change affecting sterility assurance of a sterile drug product or sterile drug substance that should be regarded as a major change, *i.e.*, requiring prior approval, should be one, which adversely affects sterility assurance. Changes, which positively affect sterility assurance, should be regarded as moderate or minor changes.

***§ 314.70(b)(2)(iv)**: Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;*

Insert the word "adversely" before "affect" to read: Changes in the synthesis or manufacture of the drug substance that may **adversely** affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;

Rationale: Changes in the synthesis or manufacture of a drug substance that improve the impurity profile should be treated as moderate or minor changes.

***§ 314.70(b)(2)(vi)**: Changes in a container closure system that controls drug delivery or that may affect the impurity profile of the drug product;*

Insert the word "adversely" before "affect" to read: Changes in a container closure system that controls drug delivery or that may **adversely** affect the impurity profile of the drug product;

Rationale: Changes in a container closure system that positively affect the impurity profile of the drug product should be treated as moderate or minor changes.

§314.70(c)(2)(i): A change in the container closure system that does not affect the quality of the final drug product;

Insert the word "adversely" before "affect" to read: A change in the container closure system that does not **adversely** affect the quality of the final drug product;

Rationale: A change in the container closure system that does not adversely affect the quality of the final product and/or positively affects the quality of the final product, should be treated as a minor change.

§314.70(c)(2)(ii)(B): Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

Insert the word "adversely" before "affect" to read: Replacement of equipment with that of similar, but not identical, design and operating principle that does not **adversely** affect the process methodology or process operating parameters.

Rationale: Replacement of equipment that does not adversely affect the process methodology or operating parameters and/or positively affects process methodology or operating parameters, should be reported as a minor change.

§314.70(c)(6)(i): Addition to a specification or changes in the methods or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

We recommend that these kinds of changes be treated as minor changes.

§314.70(c)(6)(ii): A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of product or from one container closure system to another;

Add the words "and a change in the labeled amount of product as long as the size of the container/closure system is changed proportionally." to read: A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of product or from one container closure system to another **and a change in the labeled amount of product as long as the size of the container/closure system is changed proportionally**;

Rationale: Proportional changes to a container closure system are not expected to adversely affect a drug product. We recommend that this kind of a proportional change be reported as a moderate change.

§314.70(c)(6)(iii)(C): To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product;

Replace the words "and administration" with the words "administration and storage" to read: To add or strengthen an instruction about dosage, **administration and storage** that is intended to increase the safe use of the product;

Rationale: Addition of a storage statement, which strengthens the labeling, should be treated as a moderate change.

§ 314.70(d)(2)(i): *Any change made to comply with an official compendium that is consistent with FDA requirements and provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;*

Delete all words after "compendium" to read: Any change made to comply with an official compendium.

Rationale: Upon the establishment of a USP monograph of an article, for which FDA participates in the USP approval process, USP criteria should apply to all applicants. There should be no need for an applicant to file any supplement for a change made to comply with an official compendium. All changes to an official compendium should be reported in the annual report. This will allow a level playing field for innovator and generic firms, especially when USP monographs are established after the innovator's NDA is approved. FDA's proposed language represents an increased regulatory burden for applicants.

§ 314.70(d)(2)(iii)*: Replacement of equipment with that of the same design and operating principles except for equipment used with a natural protein product, a recombinant DNA-derived protein/ polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody;*

Delete all words after "principles" to read: Replacement of equipment with that of the same design and operating principles.

Rationale: Recombinant DNA-derived protein/polypeptide products or a complex or conjugate of a drug with a monoclonal antibody are well-characterized drug products. It is reasonable to report in an annual report replacement with equipment of the same design and operating principles for these products.

§ 314.70(d)(2)(iv)*: A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form, without a change from one container closure system to another;*

Substitute the word "or" for the words "containing the same" to read: A change in the size and/or shape of a container **or** number of dosage units for a nonsterile solid dosage form, without a change from one container closure system to another;

Rationale: The applicants should determine, if a change in the number of dosage units has minimal potential to have an adverse affect upon the product. If so, the applicant should be permitted to change the number of dosage units in a container and treat this as a minor change.

§ 314.70(d)(2)(vi): *An extension of an expiration dating period based upon full shelf life data on full production batches obtained from a protocol approved in the application;*

Replace the words "full" with "production-scale" to read: An extension of an expiration dating period based upon full shelf life data on **production-scale** batches obtained from a protocol approved in the application.

Rationale: The word "full" may cause confusion, where batch scale for a product may be varied. In applications, where a range in the production scale is an approved variation, expiration dating extensions may be based upon the smallest scale, the largest scale, or any batch size in between. "Full" could be interpreted as the largest size batch of an approved batch size range and that interpretation is not correct.

§ 314.70(d)(2)(viii): *The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint;*

Delete the word "minor" to read: The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a change in an existing code imprint;

Rationale: Any change to an existing code imprint, e.g., changing from a numeric to an alphanumeric code, addition of a logo or identifying icon, changes to names, should be considered a minor change, and therefore should be reportable in the annual report.

§ 314.70(d)(3)(iii): *The date each change was made, a cross-reference to relevant validation protocols and/or SOP's, and relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product (validation).*

Delete § 314.70(d)(3)(iii).

Rationale: This section represents additional reporting requirements that are not consistent with FDAMA and are confusing and ambiguous. The reporting date each change was made is subject to confusion in interpretation. For example, an applicant may interpret the date a change was made to mean: (a) the date the product was made with the change, (b) the date the product made with the change was released by the Quality Control unit for distribution, or (c) the date the product made with the change was put into market distribution. For a labeling change, an applicant may interpret the date the change was made to include: (a) the date the label with the change was printed, (b) the date the product was labeled with the revised label, (c) the date the labeled product was released for distribution, or (d) the date the product with the revised label was put into market distribution. The only date for any change being reported in an annual report, which is meaningful, is the date that the product bearing the change was put into market distribution. The fact that an applicant has reported a change in an annual report covering the time period noted on form FDA2252 should be sufficient for Agency review.

Cross reference to relevant validation protocols and/or SOPs will cause confusion in the applicant's mind as to what validation protocols mean and what SOPs should be cross referenced. Clearly, if validation protocols and SOPs refer to the GMP requirements of product or equipment validation protocols and GMP SOPs, then these have no relevance for being submitted to the application. The only protocol that should be referred to in any annual report submission should be a comparability protocol approved by the Agency for reporting a change in an annual report.

§ 314.70(e): *Protocols. An applicant may submit one or more protocols describing the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug. Any such protocols, or changes to a protocol, shall be submitted as a supplement requiring approval from FDA prior to distribution of a drug produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect*

We welcome the Agency's inclusion of a section, which permits the applicant to submit comparability protocols to the Agency for review. We believe, however, that comparability protocols should be submitted as a "Supplement-Changes Being Effected in 30 Days."

Rationale: This reporting requirement is to provide for a reduction in regulatory burden. It should be in the interest of the applicant and Agency to further reduce regulatory burdens, wherever possible. Comparability protocols offer an outstanding data-driven means of accomplishing this goal. Reducing the time frame for implementation and review of a comparability protocol would bring much needed regulatory relief.

The addition of a comparability protocol to an application post-approval should not be the Agency's sole means of permitting this mechanism for regulatory relief. The Agency should also revise the regulations under **21 CFR 314.50(d): Content and Format of an Application** to permit and encourage the addition of comparability protocols to original applications.

On behalf of Wyeth-Ayerst Laboratories and its affiliates, we appreciate the opportunity to comment on this important proposed rule.

Sincerely,

WYETH-AYERST LABORATORIES

Vern G. DeVries, Ph.D.
Assistant Vice President
U.S. Regulatory Affairs

VDV/KFB/las:regulationscomments

PULL

ible Letter. Use twice, then recycle.

s Space

acking Label and your address label

the Tracking Label to the left of the address label.

your UPS Shipper Number or place parcel register tape above the address label.

ir Shipping Document

laybill

UPS Next Day Air
UPS Worldwide Express
Shipping Document

WEIGHT	WEIGHT	DIMENSIONAL WEIGHT	
	6 lb		

The shipper authorizes UPS to act as forwarding agent for export control and customs purposes. The shipper certifies that these commodities, technology or software were exported from the United States in accordance with the Export Administration Regulations. Diversion contrary to U.S. law is prohibited.

☐ NEXT DAY AIR ☐ WORLDWIDE EXPRESS (INTERNATIONAL)

☐ DOCUMENTS ONLY

☐ SATURDAY PICKUP ☐ SATURDAY DELIVERY

1 SHIPMENT FROM

UPS ACCOUNT NO. 46E43E

REFERENCE NUMBER

DEPT. 1012305

KAREL BERNADY

TELEPHONE 610-902-1495

WYETH AYERST MAILROOM

150 RADNOR CHESTER RD

ST DAVIDS PA 19087

2 DELIVERY TO

TELEPHONE

DOCKETS MANAGEMENT BRANCH

FOOD + DRUG ADMIN. HFA-305 RM. 1061

5630 FISHERS LANE

ROCKVILLE MD 20852

1Z 46E 43E 22 1006 328 1

1Z 46E 43E 22 1006 328 1

1Z 46E 43E 22 1006 328 1

☐ BILL RECEIVER

UPS Next Day Air®
EXTREMELY URGENT

1Z 46E 43E 22 1006 328 1

1Z 46E 43E 22 1006 328 1
TRACKING NUMBER

DELIVERY 1 EXPORT 2 EXPORT 1 DELIVERY 2
UPS LABEL FOR INTERNATIONAL SHIPMENTS

SHIPMENT ID NUMBER 46E4 3E7B CPY

DATE OF SHIPMENT 7/11/97

ABLE L
-SIZE DOCU

0101911202609 2/99 W United Parcel Service, Louisville, KY

hereunder may be subject to the rules relating to liability and other terms and/or conditions established by the Convention for the Unification of Certain Rules Relating to International Carriage by Air (the "Warsaw Convention") and/or the Convention on the Con
... in accordance with the Export Administration Regulations. Diversion contrary to U.S. law prohibited. For stopping places, call 1-800-782-7892.